DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Orphan Products Development

Memorandum

DATE: March 7, 2002

FROM: Marlene E. Haffner, MD, MPH, RADM USPHS, Director

SUBJECT: Office of Orphan Products Development (OOPD) Analysis of Exclusivity Issues Raised in the Serono BLA for Rebif

TO: Jay Siegel, MD, Director, Office of Therapeutics Research and Review, CBER

and

BLA STN 10378 / 0 FILE

Background

The Orphan Drug Act (the Act) grants seven years of exclusive marketing rights to a specific drug[1] for a specific orphan indication. The marketing exclusivity bars FDA approval during this period of the "same drug" from another sponsor for the same orphan indication. Experience has shown that this exclusivity is one of the strongest incentives in the Act for encouraging research and development of treatments for rare diseases and conditions. The importance FDA places on appropriately maintaining the value of the exclusivity incentive of the Act is reflected in the implementing regulations at 21 CFR Part 316. These same regulations also recognize the equally important need to accommodate improvements in a drug, so as to make available treatments that provide significant medical benefit.

The "Same Drug"

The orphan drug regulations adopt a definition of "same drug" that recognizes the need to give meaning to orphan exclusivity and recognition to significant therapeutic advances. Therefore, the regulations create a presumption that two drugs with similar physical/chemical characteristics are the same, and that exclusivity granted to one drug will block approval of the subsequent drug for the same indication. However, this presumption may be overcome by evidence to show that, despite the physical/chemical

[1] The Orphan Drug Act applies to both drugs approved under Section 505 of the Food, Drug, and Cosmetic Act (FDCA), and to biological products licensed under section 351 of the Public Health Service Act (PHSA). The interferon-beta products at issue are regulated under Section 351 of the PHSA. Most biological products licensed under the PHSA also meet the definition of "drug" under the FDCA. The term "drug" is used through this memo to discuss the principles of the Orphan Drug Act and the regulations.

similarity, the subsequent drug is clinically superior, and therefore is not barred by the exclusivity. Even though differences in formulation, dose, or other product characteristics by themselves do not render a drug different (that is, not the "same drug") within the orphan drug regulations, they may result in a drug being found to be different if the difference makes it clinically superior, in that it provides a significant therapeutic advantage over the product with exclusivity. The courts have found that FDA's interpretation and application of these concepts are consistent with the Orphan Drug Act. *See Baker-Norton Pharmaceuticals, Inc. v. FDA and Bristol-Myers Squibb*, 132 F.Supp. 2d 30 (D.D.C. 2001); *Berlex Laboratories, Inc. v. FDA*, 942 F.Supp. 19 (D..D.C. 1996).

Interferon beta Products

The orphan drug issues associated with the exclusivity and approval of the multiple interferon beta products for the treatment of relapsing-remitting multiple sclerosis are an example of the need to balance the value of the orphan exclusivity incentive with the availability of improved treatments for patients. The Office of Orphan Products Development (OOPD) has worked closely with CBER in the resolution of these matters. CBER's comprehensive review of the comparative study of Rebif to Avonex and orphan exclusivity describes the regulatory history of these drug products and the related orphan drug issues. OOPD believes this review correctly describes and applies the orphan drug regulations to the comparison between Biogen's Avonex and Serono's Rebif. Only a few points warrant additional discussion.

Head-to-Head Trials

Because of the agency's commitment to maintain the value of the exclusivity incentive, the requirements for demonstrating clinical superiority are stringent. The regulations require head-to-head trials in most cases for a demonstration of increased effectiveness. The requirements for safety comparisons are somewhat less rigorous because comparisons of profound adverse events may be made without a direct head-to-head clinical trial. Direct comparison trials are the standard because they eliminate the use of anecdotal evidence and prevent "apples and oranges" comparisons of dissimilar factors. However, they place a significant financial and technical burden on the sponsor of a second product. The rigor of this requirement is probably best illustrated by the fact that in the nineteen years the Act has been in existence, this matter involving multiple interferon beta treatments for relapsing-remitting multiple sclerosis is the first instance where a sponsor has attempted to challenge the exclusivity of a product by showing that its drug was more effective in a direct comparison trial.

It is also important to note that, until review of the Rebif/Avonex data, no drug product had been determined to be a different drug as a result of a head-to-head comparative trial. Avonex was found to be a different product than Betaseron based on a comparison of the safety findings in two different studies used in the approval process of two different drugs. This was possible because of the distinct nature of the adverse event at issue, and the marked difference between the two products with respect to the severity of the adverse event. However, there is no doubt Serono's study has met the more stringent standard of the type of study necessary to assess comparative efficacy.

Clinical Superiority

The orphan drug regulations clearly separate the categories of effectiveness and safety for purposes of showing clinical superiority, allowing the Agency to distinguish between two drugs by a finding of superiority in either of these categories. There is no additional requirement that the subsequent product, although clinically superior in one parameter, must also be shown to be at least equal in all others. This would set an inappropriate and nearly impossible burden (in terms of clinical trial design) on the sponsor of a second product. A more meaningful standard is a significant therapeutic benefit in terms of increased effectiveness and adequate safety, or increased safety and adequate effectiveness. The balancing of risks and benefits embodied in a drug product as a whole is done when the agency determines whether the drug may be approved for the particular use.

There is also a third approach described in the regulations for showing a significant therapeutic advantage. This requires a demonstration that, in an unusual case where neither greater effectiveness or safety has been shown, a drug otherwise makes a major contribution to patient care. This analysis may involve multiple aspects of the drug product, since the benefit to the patient is likely to be greater convenience or less discomfort, and the very term "major contribution to patient care" implies a more global assessment. So, for example, an assessment of the safety or effectiveness of the new form of the subsequent product might be considered in determining whether the drug made a major contribution to patient care. However, even in this instance, there can not be an infinite number of comparison criteria if this provision of the regulation is to be meaningful.

Given the conclusions in CBER's review, and the considerations above, OOPD believes that Serono has met the burden of establishing Rebif as not "the same drug" as Avonex because it is clinically superior in terms of efficacy. OOPD agrees that the data show a significant difference in the number of exacerbations between patients treated with Avonex and those treated with Rebif. The use of exacerbations also is a clinically meaningful measurement because these episodes represent significant suffering and hardship to the patients. As described in detail in CBER's review memorandum, the number of exacerbations is an endpoint used to establish efficacy for multiple interferon beta products and thus is well-recognized as clinically meaningful. Moreover, OOPD agrees with the CBER conclusion that the magnitude of the benefit in terms of reduced exacerbations in patients treated with Rebif represents a significant therapeutic advantage.

Safety

The difference in adverse events between Avonex and Rebif is real. For example, the injection-site necrosis observed with Rebif is not observed with Avonex. However, the adverse events do not appear to pose a serious limitation on Rebif's use. Both Rebif and Avonex would represent reasonable alternatives for the prescribing physicians and their patients.

Conclusion

OOPD concurs with CBER that Serono's Rebif may be approved for treatment of relapsing remitting multiple sclerosis because it is not the same drug as Biogen's Avonex.

cc: OPD Precedent file
J.Fritz, OPD HF35
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